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# Hepatitis C virus associated arthritis in absence of clinical, biochemical and histological evidence of liver disease – responding to interferon therapy

## Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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## Summary

### Background:

Extrahepatic manifestations associated with Hepatitis C virus (HCV) such as arthritis, vasculitis, cryoglobulinemia, are well known. However, HCV related arthritis in the absence of clinical, biochemical and histological evidence of liver disease is not common. This article deals with such a case and its response to interferon therapy.

### Case Report:

We present a case of a 32 year old Filipino male who presented with bilateral symmetrical painful swelling of multiple joints including, hands, elbows, shoulders, and knees. Serum rheumatoid factor, antinuclear antibodies and a comprehensive work-up for rheumatologic disorders were all negative. Both initially and subsequently, serological tests for hepatitis A, B, and autoimmune liver diseases, Wilson's disease, hemochromatosis, syphilis, human immunodeficiency virus (HIV) and cryoglobulinemia were negative, initially and subsequently. However, the hepatitis C antibody test was positive and hepatitis C viral RNA was detected in high titers. The joint symptoms did not improve despite therapy with nonsteroidal anti-inflammatory drugs and a short course of prednisone prescribed earlier by his primary care physician. The patient then requested and was subsequently treated with interferon alpha 2b.

### Results:

The patient responded rapidly to the interferon therapy with significant and sustained improvement in joint symptoms and disappearance of hepatitis C viral RNA from his serum.

### Conclusions:

HCV arthritis should be considered in the differential diagnosis of seronegative arthritis of undetermined etiology even in the setting of normal liver chemistries.

### key words:

**hepatitis C virus • extrahepatic manifestations • arthritis • interferon therapy**

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## BACKGROUND

Hepatitis C virus (HCV) is a major cause of significant liver disease worldwide. Approximately 170 million people are infected with HCV. It is estimated that 3.9 million people in the United States are HCV-positive; 2.7 million have evidence of HCV-RNA in their blood [1,2]. Disease caused by HCV may be multifaceted and not always be limited to the liver [3]. The list of reported extrahepatic manifestations associated with HCV disease, is growing progressively. These manifestations include: membranoproliferative glomerulonephritis [4], cryoglobulinemia [5], porphyria cutanea tarda [6], vasculitis [7] lymphocytic sialadenitis with or without sicca syndrome [8], lichen planus [9], autoimmune thyroiditis [10], aplastic anemia [11], pancreatitis [12], pancreatic lymphadenopathy [13], arthritis [14,15] myalgia [16], fibromyalgia [17], neuropathy [18,19], pruritus [20,21], fatigue [22], lymphoma [23], corneal ulcer [24], idiopathic pulmonary fibrosis [25] and possibly type II diabetes mellitus [26]. Symptoms related to cryoglobulinemia may be improved with interferon alpha treatment [27].

## CASE REPORT

We present the case of a thirty two year old Filipino male who was referred by his primary care physician with a history of an abrupt onset bilateral painful swelling of small joints of both hands, wrists, elbows, knees, and ankle joints which has persisted for four weeks. No other significant symptoms were present except fatigue. There was no history of skin rashes, eye problems, oral or genital ulcers, diarrhea or any other urogenital complaints. Patient denied any fever or chills, recent travel or exposure to ticks. There was no history of high risk sexual behavior, intravenous drug abuse, or previous history of blood transfusion, jaundice or exposure to a patient with hepatitis. The past medical history and family history was non-contributory. The physical examination was non-contributory except bilateral symmetrical swelling of joints of hands, wrists, elbows, shoulders, knees, ankles and feet. Movements of involved joints were painful but there was no definite restriction in the range of movements and there were no joint deformities or contractures. Radiographs of involved joints revealed soft tissue swelling and effusion but no evidence of bony erosions, chondrocalcinosis or deformity.

Skin rashes or subcutaneous nodules or tophi were absent. Upon arthrocentesis of the right knee joint 9 ml of yellow colored translucent fluid was obtained. Synovial fluid studies revealed total white blood cells 245/ $\mu$ L, polymorphonuclear neutrophil 60/ $\mu$ L, and glucose 75 mg/dL, (blood glucose 80 mg/dL). No crystals were detected in the synovial fluid and cultures were negative. Standard tests for rheumatologic disorders including (ANA, Anti-Sm Ab, anti-dsDNA, Anti RNP Ab, Anti-Centromere Ab, Anti-Ro Ab, and Anti-Histone Abs) were negative initially and subsequently. Serological tests for syphilis, human immunodeficiency virus (HIV), hepatitis A, hepatitis B and cryoglobulinemia were also negative initially and remained negative throughout the period of follow-up.

Laboratory tests including liver chemistry (alanine aminotransferase, albumin, alkaline phosphatase, and bilirubin), complete blood count, and erythrocyte sedimentation rate,

and serum uric acid, were all normal initially and remained so at all subsequent follow-up visits. However, the HCV antibody test was positive and quantitative estimation of hepatitis C viral RNA revealed 550,000 viral equivalents/ml. HCV genotype was identified as 1b.

A liver biopsy revealed normal liver histology, with no evidence of inflammation, fatty infiltration or fibrosis. The patient reported no significant improvement in his joint symptoms, despite therapy with various nonsteroidal anti-inflammatory drugs, including ibuprofen, naproxen and meloxicam, followed by a short (7-day) course of prednisone prescribed by his primary care physician. The patient insisted on having anti-HCV therapy. He was treated with interferon alpha 2b, 300 million units three times weekly. Within two week of the initiation of interferon therapy significant improvement was noticed in joint pain and swelling. The pain and swelling of all joints completely disappeared completely after three months of interferon therapy. However, the therapy was continued for six months. Hepatitis C viral RNA titers progressively decreased and were undetectable after six months of therapy and for eighteen months thereafter.

## DISCUSSION

The occurrence of arthritis during the early phase of many viral diseases including viral hepatitis is a well-known phenomenon. Arthralgias are common in patients with HCV; however, overt arthritis occurs less frequently. Reactive arthritis has been observed following genitourinary and gastrointestinal infections. The exact pathogenesis of reactive arthritis including HCV associated arthritis remains to be elucidated. However, speculations on the mechanism include, virus induced immune modulation, autoimmunity, direct invasion of synovial cells by the virus, a combination of more than one or yet unknown factor (s) [28,29]. One of the common extrahepatic manifestations of HCV infection is mixed cryoglobulinemia, which may manifest clinically as palpable purpura, glomerulonephritis, neuropathy and arthritis.

Liakina et al. [30] described a high prevalence of cryoglobulinemia and its association with extrahepatic manifestations, in their study of Lithuanian patients with HCV infection. In our patient, cryoglobulinemia was not detected on serial testing, nor were there any clinical evidence of associated manifestations other than arthritis.

Brillanti et al. [31] reported on four individuals with HCV viremia, a normal liver biopsy and liver chemistry who remained symptom-free over three years of follow-up in contrast to our patient who presented with arthritis. It is not very clear whether the extrahepatic conditions are a direct result of HCV infection or are manifestations of the liver disease.

The course of illness in our patient, including response to anti-HCV therapy and the absence of liver disease, suggests that extrahepatic conditions may be the direct result of HCV infection.

Although there was no definitive evidence of a causal relationship between arthritis and HCV infection in our patient, a comprehensive evaluation, including joint radiographs,

standard tests for rheumatologic disorders and synovial fluid studies, failed to reveal an alternative etiology for the arthritis. Fluctuating transaminase levels are common during HCV infection. Ohmiya [32] reported a series of patients with normal transaminases and HCV-RNA viraemia. He showed that patients with normal transaminases do respond to interferon treatment with reduction in quantitative HCV-RNA viraemia. Transaminase levels were found to be consistently normal in our patient. The absence of liver disease in our patient cannot be explained precisely. Possibilities include, arthrotrophic behavior of this strain of HCV, extrahepatic replication of HCV [33] or yet an undetermined host-related immunologic phenomenon. Active HCV replication may occur in some patients in the absence of any evidence of liver disease. These patients may respond to interferon alpha, which has been shown to be a safe and effective [32,34].

## CONCLUSIONS

We conclude that HCV arthritis should be considered in the differential diagnosis of seronegative arthritis of undetermined etiology, even in the absence of clinical, biochemical and histological evidence of liver disease.

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